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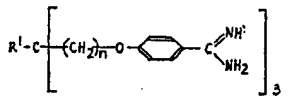
(54) POLY-p-AMIDINOPHENOXY ALKANES

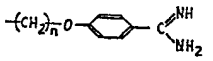
(71) We, MINNESOTA 3M LABORATORIES LIMITED, a British Company, of Morley Street, Loughborough, Leicestershire, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to poly-*p*-amidinophenoxy alkanes and their preparation.

According to the invention there is provided a poly-*p*-amidinophenoxy alkane having the general formula:—



wherein R^1 is a hydrogen atom, a lower alkyl group or a *p*-amidinophenoxy group having the general formula:—



and wherein all the n's are the same and each n is 0 or an integer of from 1 to 6, provided that n is not 0 when R^1 is a *p*-amidinophenoxy group, and wherein the aromatic nucleus in each *p*-amidinophenoxy group may bear one or more lower alkyl, lower alkoxy, halo or trifluoromethyl substituents provided that all the *p*-amidinophenoxy groups are identical.

Preferably each n is an integer of from 1 to 6.

As used throughout this specification and appended claims the terms "lower alkyl" and "lower alkoxy" embrace both straight and branched chain alkyl and alkoxy radicals, respectively, containing from 1 to 6 carbon atoms, for example methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, n-amyl, sec-amyl, n-hexyl, 2-ethylbutyl and 2,3-dimethylbutyl in the case of lower alkyl and methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, tert-butoxy, n-amoxy, sec-amoxy, n-hexyloxy, 2-ethylbutoxy and 2,3-dimethylbutoxy in the case of lower alkoxy and the term "halo" embraces chloro, bromo, iodo and fluoro.

The compounds of the present invention are solid crystalline materials. Elemental analysis, infra-red spectral and nuclear magnetic resonance data, taken together with the nature of starting materials and mode of synthesis, positively confirm the structures of the compounds.

The compounds of the present invention inhibit *in vitro* the "cancer coagulation factor" produced by Walker Carcinoma in Wistar rats and also inhibit *in vivo* the growth of Sarcoma 180 tumors implanted in hybrid mice by procedures hereinafter described.

The compounds of the present invention can, if desired, be converted into their acid-addition and quaternary ammonium salts. Salts which may be formed comprise, for example, salts with inorganic acids, such as the hydrochloride, hydrobromide, hydroiodide, sulphate and phosphate. They may also comprise salts with organic acids, including monobasic acids such as the acetate or the propionate, and especially those with hydroxy organic acids and polybasic acids, such as the citrate, tartrate, malate and maleate. Among the useful quaternary ammonium salts are those formed by such alkyl halides as methyl iodide and n-hexylbromide. Such acid-addition and quaternary ammonium salts may be employed in like manner as the bases from which they are derived.

The invention also provides a method of treating animals other than homo sapiens which method comprises administering thereto a poly-*p*-amidinophenoxy alkane in accordance with the present invention, a pharmaceutically acceptable acid addition salt thereof or a pharmaceutically acceptable quaternary ammonium salt thereof or any mixture thereof.

The invention also provides a method of preparing a poly-*p*-amidinophenoxy alkalne as

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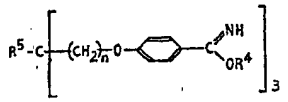
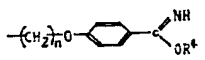
defined above which comprises treating with ammonia an imino-ether of the formula:

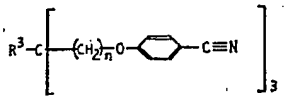


wherein R^4 is a lower alkyl group and R^5 is a hydrogen atom, a lower group, or a group having the formula:



and wherein all the n's are the same and each n is 0 or an integer of from 1 to 6 provided that n is not 0 when R^5 is a *p*-iminoetherphenoxy group, and wherein the aromatic nucleus of each *p*-iminoetherphenoxy group may bear one or more lower alkyl, lower alkoxy, halo or trifluoromethyl substituents provided that all of the *p*-iminoetherphenoxy groups are identical.

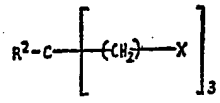
An imino ether as defined above may be prepared by a method which comprises treating a poly - *p* - cyanophenoxy alkane having the general formula:



wherein R^3 is a hydrogen atom, a lower alkyl group or a *p*-cyanophenoxy group having the general formula:—

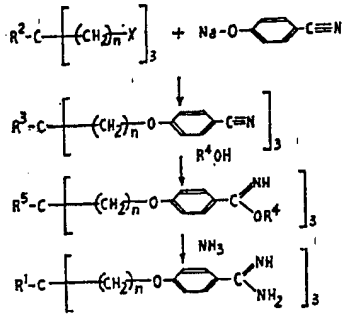
and wherein all the n's are the same and each n is 0 or an integer of from 1 to 6 provided that n is not 0 when R^3 is a *p*-cyanophenoxy group, and wherein the aromatic nucleus of each *p*-cyanophenoxy group may bear one or more lower alkyl, lower alkoxy, halo or trifluoromethyl substituents, provided that all of the *p*-cyanophenoxy groups are identical, with an acidified alkanol of from 1 to 6 carbon atoms under anhydrous conditions in the presence of an inert organic solvent.

A poly-*p*-cyanophenoxy alkane as defined above is described and claimed in copending application No. 51480/68 (Serial No. 1,288,377), which also describes and claims a method for its preparation which comprises (a) refluxing an alkali metal derivative of *p*-hydroxybenzonitrile, the aromatic nucleus of which may bear one or more lower alkyl, lower alkoxy, halo or trifluoromethyl substituents, with a polyhaloalkane having the general formula:—



wherein R^2 is a hydrogen atom, a lower alkyl group or the atom X and each X is a bromine or iodine atom, in a solvent, there being at least one mole of alkali metal derivative of *p*-hydroxybenzonitrile present for each mole of halogen present in the polyhaloalkane.

A preparation of the compounds of the present invention may thus be illustrated by the following reaction scheme:—



The polyhaloalkane starting materials described in the foregoing reaction scheme are known compounds that are commercially available or are, together with methods for their preparation, disclosed in the chemical literature. They may readily be prepared, for example from their corresponding polyhydroxy alkanes by conventional halogenation procedures, e.g. bromination with phosphorus tribromide. The preparation of 1-bromo-2,2-bis(bromomethyl)butane from the corresponding 2,2 - bis(hydroxymethyl) - n - butanol by treatment with phosphorus tribromide is described by Derfer et al, J. Am. Chem. Soc. 67:1863 (1945), and the preparation of 2,2-bis(bromomethyl) - 1,3 - dibroompropane (pentaerythrityl tetrabromide) from pentaerythritol by the same technique is described in Rev. trav. chim, 50:921—30 (1931). Similarly the sodium derivative of *p*-hydroxybenzonitrile described in the foregoing reaction scheme is a known, commercially available, compound. Alkali metal derivatives other than sodium, for example the potassium and lithium derivative may be substituted in the reaction scheme for the sodium derivative of *p*-hydroxybenzonitrile.

Starting materials wherein the aromatic nucleus of the alkali metal derivative of *p*-hydroxybenzonitrile bear one or more lower alkyl, lower alkoxy, halo or trifluoromethyl radicals may be substituted in the foregoing reaction scheme in place of alkali metal derivatives of *p*-hydroxybenzonitrile wherein the aromatic nucleus is unsubstituted. The use of such substituted starting materials results in the preparation of intermediates and final products bearing lower alkyl, lower alkoxy, materials, such final products having the same position or positions as in the starting

materials, such final products having the same utility as poly-*p*-amidinophenoxy alkanes bearing no substituents on the aromatic nuclei.

The solvent in which the polyhaloalkane and the alkali metal derivative of the *p*-hydroxybenzonitrile and refluxed preferably has a boiling point which is high, that is to say sufficently high that the rate of reaction, at the reflux temperature, is not inconveniently low. Normally the boiling point of the solvent is at least 150°C, preferably in the range of 150°C to 220°C, for example benzonitrile or dimethyl formamide. The reaction can be carried out under a nitrogen atmosphere. The poly-*p*-cyanophenoxy alkane intermediate may be separated by conventional techniques of isolation and crystallisation.

The poly-*p*-cyanophenoxy alkane intermediates may be converted to poly-*p*-amidinophenoxy alkanes first by treatment with an acidified alkanol of from 1 to 6 carbon atoms, for example methanol, ethanol, n-propanol or isopropanol under anhydrous conditions in the presence of an inert organic solvent, for example chloroform, to form the corresponding imino ether. The imino ether thus formed need not be purified, but may be converted, after crude separation, into a poly-*p*-amidinophenoxy alkane final product by treatment with ammonia, the reaction readily taking place at room temperature. The final product may be isolated and purified by conventional methods.

The invention will now be illustrated with reference to the following Examples.

Example 1.

a) 1 - *p* - Cyanophenoxy - 2,2 - bis - (*p* - cyanophenoxymethyl)butane.

Sodium *p*-cyanophenate (45 g.) and 1-bromo - 2,2 - bis(bromomethyl)butane (30 g.) were refluxed together in benzonitrile (250 ml.). After filtering the hot mixture to remove the sodium bromide formed, most of the benzonitrile solvent was removed by vacuum distillation. The residue was poured into ether (1000 ml.). Remaining sodium bromide was removed and the ethereal solution was diluted with an equal volume of petroleum ether. This caused the product to precipitate as an oil which solidified upon trituration with methanol. The solid was recrystallised from methanol and decolorised over charcoal to yield 34.2 g. of white needles, m.p. 93—95°C.

Analysis:
Calculated for $C_{27}H_{23}N_3O_3$: C, 74.1%; H, 5.3%; N, 9.6%
Found: C, 73.8%; H, 5.5%; N, 9.7%

b)1 - *p* - Amidinophenoxy - 2,2 - bis - *p*-amidinophenoxymethyl)butane.

The tri-cyanophenoxy compound (32 g.) formed as described in "a" above, was dissolved in a mixture of anhydrous chloroform (150 ml.) and anhydrous ethanol (30 ml.), cooled to 5°C and saturated with hydrogen chloride gas. The reaction was allowed to proceed at room temperature, the rate of conversion to the ethylimino ether being followed by measuring the drop in intensity of the infra-red —C≡N band. After presence of a —C≡N band was no longer detectable the ethylimino ether product was precipitated by pouring into anhydrous ether. The precipitated solid was dried *in vacuo* at 40°C and then added to an ice cold solution of ammonia in methanol (10%, 250 ml.) and then kept at room temperature for 40 hours. The alcoholic ammonia was distilled off *in vacuo* and the residue shaken with 1 N. sodium hydroxide solution to give a gummy deposit. This material was recrystallised from 2 N. aqueous HCl. to yield 19.5 g. of product in the form of a trihydrochloride trihydrate, m.p. 220—222°C.

Analysis:
Calculated for $C_{27}H_{32}N_6O_3.3HCl.3H_2O$: C, 49.7%; H, 6.3%; N, 12.9%; Cl, 16.1%
Found: C, 50.2%; H, 6.4%; N, 12.7%; Cl, 16.3%

Example 2.

a) 1,3 - Di - (*p* - Cyanophenoxy) - 2,2 - bis-(*p* - cyanophenoxymethyl)propane.

Pentaerythritol tetrabromide (14.9 g.) and sodium *p*-cyanophenate (26 g.) were refluxed together in benzonitrile (100 ml.) under the same conditions as described in Example 1a to yield 15.1 g. of crystalline product, m.p. 222—224°C.

Analysis:
Calculated for $C_{33}H_{24}N_4O_4$: C, 73.3%; H, 4.5%; N, 10.4%
Found: C, 72.8%; H, 4.5%; N, 10.4%

b) 1,3 - Di - (*p* - amidinophenoxy) - 2,2-bis - (*p* - amidinophenoxymethyl)propane.

The tetra-cyanophenoxy compound prepared in "a" above was treated as described in Example 1b to yield 19.4 g. of product in the form of a tetrahydrochloride tetrahydrate, m.p. 232—236°C.

Analysis:
Calculated for $C_{33}H_{36}N_8O_4.4HCl.4H_2O$: C, 48.0%; H, 5.9%; N, 13.6%; Cl, 17.1%
Found: C, 48.2%; H, 5.6%; N, 13.2%; Cl, 16.9%

The inhibitory effect of the polyamidinophenoxy alkanes according to the present invention both *in vitro* on the "cancer coagulation factor" produced by Walker Carcinoma in Wistar rats and *in vivo* on the growth of implanted Sarcoma 180 tumors in hybrid mice was determined using protamine sulphate as a known standard inhibitor. The following tests illustrate the procedures employed and the results obtained.

Test 1.

Acute toxicity determinations, in accordance with standard pharmacological test procedures, made for the compounds used in the following Tests 2 and 3 revealed the following: (These compounds will be identified hereinafter by the letters A, B and C as used in this table).

A. Protamine sulphate standard: *
LD_{50} mice: 250 mg./kg. (subcutaneous)
LD_{50} mice: 94 mg./kg. (intraperitoneal)

B. 1 - *p* - Amidinophenoxy - 2,2 - bis(*p* - amidinophenoxymethyl) butane:
LD_{50} mice: 112 mg./kg. (subcutaneous)
LD_{50} mice: 47 mg./kg. (intraperitoneal)

C. 1,3 - di - (*p* - Amidinophenoxy) - 2,2 - bis(*p*-amidinophenoxymethyl) propane:
LD_{50} mice: 110 mg./kg. (subcutaneous)
LD_{50} mice: 50 mg./kg. (intraperitoneal)

* LD_{50} values for protamine sulphate are those reported by L. Reiner et al, Proc. Soc. Exptl. Biol. Med. *50*:70—4 (1942).

Test 2.

In Vitro Anti-Cancer Coagulation Factor.

At the growing edge of malignant tissues a fibrin is laid down ahead of the growth that according to O'Meara (Irish J. Med. Sci, *1958*, p. 474) is produced by a "cancer coagulation factor" in the cancer cells. This "cancer coagulation factor" is inhibited by protamine sulphate (Thornes and O'Meara, Irish J. Med. Sci, *1961*, pp. 361—365). Using protamine sulphate as a standard, the polyamidinophenoxy alkanes according to the present invention were evaluated for their ability also to inhibit "cancer coagulation factor". The method used was a modification of that described by O'Meara (Irish J. Med. Sci, *1958*, p. 474) and Boggust et al (Irish J. Med. Sci, *1963*, p. 131).

A "cancer coagulation factor" extract from a Walker Carcinoma in the Wistar rat was diluted to double the concentration at which it was known to produce clotting of a calcified plasma buffered substrate in less than 6 minutes.

This diluted "cancer coagulation factor" (0.5 ml.) was measured into each of a series of sterile plastic test tubes. To the first tube of the series was added a solution (0.5 ml.) of the compound to be tested. After thorough mixing 0.5 ml. of the mixture was added to the "cancer coagulation factor" solution in the next tube.

This operation was repeated until the desired number of dilutions of the test compound in "cancer coagulation factor" extract had been set up. After mixing the mixture in the last tube, 0.5 ml. of the mixture was discarded. The series of tubes, each containing 0.5 ml. of a mixture of equal parts of "cancer coagulation factor" extract and test compound at various concentrations was incubated for 30 minutes at 37°C. After 30 minutes, the tubes containing the mixtures were cooled rapidly in the refrigerator at 4°C, and, when cool, 0.3 ml. of calcium chloride solution was added. The concentration of the calcium chloride solution (1.25% by weight) was that which had already been found by the Boggust et al (Irish J. Med. Sci, *1963*, pp. 131—144) technique to be the optimum for titrating "cancer coagulation factor" with the particular plasmas buffered substrate being employed in the test.

Following the addition of the calcium

chloride solution, 0.5 ml. of the plasma buffered substrate was added and the rack of tubes returned to the 37°C water bath. The clotting time of each mixture during incubation was then noted.

In these tests two controls were used, plasma and an untreated "cancer coagulation factor" control. In the plasma control, the mixture of "cancer coagulation factor" and compound under test was replaced with 0.5 ml. of distilled water. The untreated "cancer coagulation factor" control consisted of 0.5 ml. of the "cancer coagulation factor" extract only diluted 1:2 with distilled water. At least three tubes of each control type were employed in each test and these were treated in precisely the same manner as the test solution.

The results of this test were as follows:

Clotting Time in Minutes at 37°C, 30 Minutes After the Mixing of Test Compound with 16 Protamine Sulphate Equivalent Units of Cancer Coagulation Factor*

Dilution of Compound	Untreated "Cancer Coagulation Factor"	Compound A	Compound B	Compound C
1/4000	5	No Clot	No Clot	No Clot
1/8000	4	No Clot	No Clot	No Clot
1/16000	5	No Clot	17	18
1/32000	—	No Clot	9	9
1/64000	—	15	8	7

*A Protamine Sulphate Equivalent unit is defined as that amount of coagulation factor from a malignant tumor which is neutralised by one microgram of protamine sulphate.

The results of this test show both compounds B and C to have inhibitory activity against the "cancer coagulation factor" produced by Walker Carcinoma in Wistar rats equal to about one-half that exhibited by compound A, the known inhibitor protamine sulphate.

Test 3.

In Vivo Inhibition of Sarcoma 180 Tumor Growth.

Twenty-four hybrid mice of approximately 24 grams weight each were implanted with small pieces of Sarcoma 180. The Sarcoma 180 tumor material was originally obtained from the Chester Beatty Research Institute in London, and maintained through more than fifty passages in the breed of mice used. The mice used were laboratory bred hybrids. The tumor fragments from donor mice were implanted subcutaneously into the mice by trocar. The animals were then separated into three groups of eight animals each and treated as follows:

Group I—Received on the 3rd, 4th, 5th and 6th days after implantation 0.1 ml. physiological saline by intraperitoneal injection.

Group II—Received on the 3rd, 4th, 5th and 6th days after implantation protamine sulphate in physiological saline at a dose of 16.8 mg./kg. administered intraperitoneally. Protamine sulphate was used as a standard control because of its known inhibitory effect upon tumor growth (Muggleton et al, Lancet No. 7730, *1964*, pp. 409—410).

Group III—Received on the 3rd, 4th, 5th and 6th days after implantation 1-p-amidinophenoxy - 2,2 - bis(p - amidinophenoxymethyl)butane in physiological saline at a dose of 16 mg./kg. administered intraperitoneally.

On the seventh day the animals were euthanized and the tumors dissected out and weighed. The results of this test were as follows:

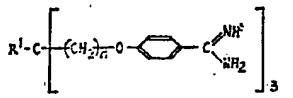
Weight in Grams of Developed Sarcoma 180 Tumors in Hybrid Mice Seven Days After Implantation of Tumor Fragment

Group	No. of Mice	Tumor Weight in Grams ± S.E.
I	8	0.468 — 0.017
II	8	0.423 — 0.029
III	8	0.319 — 0.036

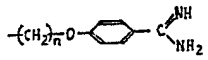
This experiment shows the pronounced inhibition of Sarcoma 180 Tumor growth in hybrid mice by 1 - *p* - amidinophenoxy - 2,2-bis - (*p* - amidinophenoxymethyl) butane (Group III) to be considerably superior to that exhibit by the known inhibitor protamine sulphate (Group II).

WHAT WE CLAIM IS:—

1. A poly - *p* - amidinophenoxy alkane having the general formula:—



wherein R^1 is a hydrogen atom, a lower alkyl group or a *p*-amidinophenoxy group having the general formula:—



and wherein all the n's are the same and each n is 0 or an integer of from 1 to 6, provided that n is not 0 when R^1 is a *p*-amidinophenoxy group, and wherein the aromatic nucleus in each *p*-amidinophenoxy group may bear one or more lower alkyl, lower alkoxy, halo or trifluoromethyl substituents, provided that all of the *p*-amidinophenoxy groups are identical.

2. 1 - *p* - Amidinophenoxy - 2,2 - bis - (*p*-amidinophenoxymethyl) butane.

3. 1,3 - di - (*p* - amidinophenoxy) - 2,2-bis - (*p* - amidinophenoxymethyl)propane.

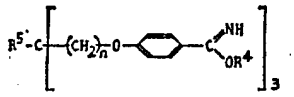
4. An acid-addition salt or quaternary ammonium salt of a poly - *p* - amidinophenoxy alkane as claimed in any one of the preceding claims.

5. An acid-addition salt as claimed in claim 4 which is the hydrochloride, hydrobromide, hydroiodide, sulphate or phosphate salt or the salt of a monobasic or polybasic organic acid.

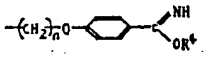
6. An acid-addition salt as claimed in claim 5 which is the acetate, propionate, citrate, tartrate, malate or maleate salt.

7. A quaternary ammonium salt as claimed in claim 4 which is the salt formed with methyl iodide or n-hexyl - bromide.

8. A method for preparing a poly-*p*-amidinophenoxy alkane according to claim 1 which comprises treating with ammonia an imino-ether of the formula:



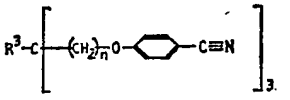
wherein R^4 is a lower alkyl group and R^5 is a hydrogen atom, a lower alkyl group, or a group having the formula:



and wherein all the n's are the same and each n is 0 or an integer of from 1 to 6 provided that n is not 0 when R^5 is a *p*-imino-etherphenoxy group, and wherein the aromatic nucleus of each *p*-iminoetherphenoxy group may bear one or more lower alkyl, lower alkoxy, halo or trifluoromethyl substituents provided that all of the *p*-iminoetherphenoxy-groups are identical.

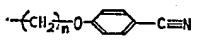
9. A method as claimed in claim 8 wherein the imino ether is treated with ammonia at room temperature.

10. A method according to claim 8 or 9 wherein the said imino ether is one formed by a method which comprises treating a poly-*p*-cyanophenoxy alkane having the general formula:



wherein R^3 is a hydrogen atom, a lower alkyl

group or a *p*-cyanophenoxy group having the general formula:—

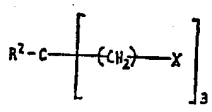


and wherein all the n's are the same and each n is 0 or an integer of from 1 to 6 provided that n is not 0 when R^3 is a *p*-cyanophenoxy group, and wherein the aromatic nucleus of each *p*-cyanophenoxy group may bear one or more lower alkyl, lower alkoxy, halo or trifluoromethyl substituents, provided that all of the *p*-cyanophenoxy groups are identical, with an acidified alkanol of from 1 to 6 carbon atoms under anhydrous conditions in the presence of an inert organic solvent.

11. A method as claimed in claim 10 wherein the alkanol is methanol, ethanol, n-propanol or iso-propanol.

12. A method as claimed in claim 10 or 11 wherein the inert organic solvent is chloroform.

13. A method according to any of claim 10 to 12 wherein the said poly-*p*-cyanophenoxy alkane is one formed by a method which comprises (a) refluxing an alkali metal derivative of *p*-hydroxybenzonitrile, the aromatic nucleus of which may bear one or more lower alkyl, lower alkoxy, halo or trifluoromethyl substituents, with a polyhaloalkane having the general formula:—



wherein R^2 is a hydrogen atom, a lower alkyl group or the atom X and each X is a bromine or iodine atom, in a solvent, there being at least one mole of alkali metal derivative of *p*-hydroxybenzonitrile present for each mole of halogen present in the polyhaloalkane.

14. A method as claimed in claim 13 wherein the alkali metal derivative of *p*-hydroxybenzonitrile is the sodium, potassium or lithium derivative.

15. A method as claimed in claim 13 or claim 14 wherein the polyhaloalkane is a polybromoalkane prepared by treating the corresponding polyhydroxyalkane with phosphorus tribromide.

16. A method as claimed in any one of claims 13 to 15 wherein the reaction of the polyhaloalkane with the alkali metal derivative of *p*-hydroxybenzonitrile is carried out under a nitrogen atmosphere.

17. A method as claimed in any one of claims 13 to 16 wherein the reflux solvent has a boiling point in the range of from 150°C to 220°C.

18. A method as claimed in claim 17 wherein the reflux solvent is benzonitrile.

19. A method as claimed in any one of claims 13 to 16 wherein the reflux solvent has a boiling point of at least 150°C.

20. A method as claimed in claim 19 wherein the reflux solvent is dimethyl formamide.

21. A method of preparing a poly-*p*-amidinophenoxy alkane substantially as hereinbefore described with reference to Example 1 or Example 2.

22. A poly-*p*-amidinophenoxy alkane whenever prepared by the method claimed in any one of claim 8 to 18 and 21.

23. A poly-*p*-amidinophenoxy alkane whenever prepared by the method claimed in claim 19 or claim 20.

24. A method of treating animals other than homosapiens, which method comprises administering thereto a poly-*p*-amidinophenoxy alkane as claimed in any one of claims 1 to 3 and 22, a pharmaceutically acceptable acid addition salt as claimed in any one of claims 4 to 6, a pharmaceutically acceptable quaternary ammonium salt as claimed in claim 4 or claim 7 or any mixture thereof.

25. A method of treating animals other than homosapiens, which method comprises administering thereto a poly-*p*-amidinophenoxy alkane as claimed in claim 23.

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